REMARKS

Claims 8, 9 and 30-36 are pending in this application. Claims 8, 9 and 30-36 are rejected. By the present amendment, claims 8, 9, and 30 are hereby amended, claim 31 is hereby canceled without prejudice or disclaimer, and new claims 37 and 38 are hereby added. The specification has also been amended to correct typographical errors, to note trademarks, and to add Sequence Identifiers to Figures 2, 3, 5, 6, and 13. As the amendments and new claims are fully supported by the application as filed, the amendments and new claims add no new matter.

In view of the amendments and following remarks, reconsideration of claims 8, 9, 30, and 32-36 and consideration of new claims 37 and 38 are respectfully requested.

Objections to the Specification

As requested by the Patent Office, applicants have amended the specification to indicate that the terms QUIKchange, GeneChips and TOPflash are trademarks. In addition, as requested by the Patent Office, applicants have amended the specification to provide sequence identifiers for the sequences disclosed in Figures 2, 3, 5, 6, and 13. Applicants, however, did not find primer sequences on pages 55-56 and 59.

Claim Objections

As requested by the Patent Office, Claim 8 has been amended to indicate that the amino acid sequence is set forth in SEQ ID NO: 2 rather than in Figure 2 of the application. Applicants submit that the amendment overcomes the objection.

§ 112 Rejections

Claims 8, 9 and 30-36 are rejected under 35 USC § 112, second paragraph, "as being indefinite." (See Page 4 of the Office Action.)

Claim 31 has been canceled rending the rejection of this claim moot. Claim 8 has been amended and no longer recites the phrase "capable of" or that the DNA molecule hybridizes "under stringent conditions". Claim 8, which also now lists three ligands previously included in claim 9, recites the full name, i.e., dickkopf, of the dkk protein. Claim 30 has been amended to indicate that BSMR is an acronym for bone strength and mineralization regulator. Applicants submit that claims 8, 9, 30, 32-36, as amended, are definite.

§102 Rejections

Claim 8, 30, and 31 are rejected under 35 USC 102 (e) as being anticipated by Carulli et al. (U.S. Patent NO. 6,780,609)(hereinafter "Carulli et al.")

Claim 8 has been amended to recite that the ligand that is administered is a human Wnt protein, a 36 kDa frizzled related protein, or a dickkopf (dkk) protein. Carulli et al. does not disclose using any of these three ligands to regulate bone strength and mineralization. Lacking such a disclosure, Caurlli et al. does not anticipate claim 8.

Claim 31 has been canceled rendering rejection of this claim moot, and claim 30 has been amended to recite a method of treating osteoporosis in a human patient that comprises administering an amount sufficient to increase alkaline phosphatase activity of bone forming cells of the following BSMR effectors: WNT1, WNT2, WNT2B/13, WNT3, WNT3A, WNT4, WNT5A, WNT5B, WNT6, WNT7A, WNT7B, WNT8A, WNT8B, WNT10A, WNT10B, WNT11, WNT14, WNT15, WNT16, the 36 kDa cysteine rich frizzled related protein Frzb--1, a cysteine rich protein from the CCN family7, Mus musculus FK506 binding protein 8, Mus musculus nuclear protein 95 (Np95); GLI-Kruppel family member GLI3, Mus musculus RAN binding protein 9, Mus musculus ISL1 transcription factor, Human signal-transducing guanine nucleotide-binding regulatory (G) protein beta subunit, Mus musculus, casein kinase II, Homo sapiens zinc finger protein 198, Mus musculus, eukaryotic translation elongation factor 2, M. musculus P311, Homo sapiens E2a--Pb.times.1-associated protein, Homo sapiens NADH dehydrogenase (ubiquinone) Fe--S protein 8, Human Smad anchor for receptor activation (SARA), Homo sapiens AMSH, and ATP6B2. Carulli et al does not disclose treating osteoporosis with any of these BSMR effectors. Lacking such a disclosure Carulli et al. does not anticipate claim 30.

§ 103 Rejections

Claims 31-32 are rejected under 35 USC 103 (a) as being unpatentable over Carulli et al. in view of Pinson et al. (Nature (2000) 407: 535-538) (hereinafter "Pinson et al.")

Since claim 31 has been canceled, and claim 30 has been amended to recite a method of treating osteoporosis by administering to the patient an amount of a BSMR (i.e., LRP5) effector

sufficient to increase alkaline phosphatase activity in bone forming cells, wherein the effector is chosen from a number of BSMR effectors including WNT1, WNT2, WNT2B/13, WNT3, WNT3A, WNT4, WNT5A, WNT5B, WNT6, WNT7A, WNT7B, WNT8A, WNT8B, WNT10A, WNT10B, WNT11, WNT14, WNT15, WNT16, applicants will address this rejection as it applies to claim 30 and 32.

Carulli et al recites the sequence of a gene referred to as Zmax1 by Carulli et al. and the sequence of a mutant form of the Zmax 1 gene named HBM by Carulli et al. (See col. 6, lines 15-25 of Caurlli et al.) Carulli et al also states that:

> Zmax1 and HBM interact with several proteins such as ApoE. Molecules that inhibit the interaction between Zmax1 or HBM and Apo E or another binding partner are expected to **alter** bone development and mineralization. Such drugs may be useful in the treatment or osteo**porosis,** osteo**petrosis,** or other diseases of bone mineralization. (See col. 84, lines 54-59, emphasis added.)

Carulli et al. does not teach or suggest that any of the BSMR effectors recited in claim amended claim 30, including WNT, is a binding partner for Zmax1, (i.e., LRP5) or that any of the BSMR effectors recited in claim 1, including WNT would inhibit the interaction between Zmax1 and ApoE or between Zmax1 and another binding partner. Moreover, as shown in the above-quoted statements Carulli et al. does not indicate which, if any, of the several molecules that interact with or that "inhibit" the interaction between Zmax1 and one of its binding partners will increase bone development and mineralization or which, if any, of the several molecules that interact with or inhibit the binding of Zmax1 to one of its binding partner will decrease bone development and mineralization. Thus, one of ordinary skill in the art, upon reading Carulli et al., would understand that some of the molecules that bind to Zmax1 could have a positive effect, some could have a negative effect, and some could have no effect on alkaline phosphatase activity in bone forming cells. Similarly, Carulli et al. does not teach or suggest which "inhibitors" of binding between Zmax1 and one of its binding partner or which binding partners of Zmax1 could serve as therapeutic agents for osteoporosis and which could serve as therapeutic agents for osteopetrosis, a disease that involves excess bone deposition and is therefore the exact opposite of osteoporosis, a disease that involves insufficient bone deposition. Thus, one of ordinary skill in the art, upon reading Carulli et al. would understand that some of molecules that bind to Zmax1 could have a beneficial effect, some could have a detrimental effect, and some

could have no effect on osteoporosis. Finally, Carulli et al. does not teach or suggest any molecules other than ApoE that bind to Zmax1.

Pinson et al. does not provide the teachings or suggestions missing from Carulli et al. In other words, Pinson et al. does not teach or suggest that Wnt proteins activate BSMR (LRP5) in bone forming cells, i.e., osteoblasts. Pinson et al. is directed to the arrested development of mouse embryos with an insertion mutation in the gene that encodes LRP6, a protein that has only 71% homology with LRP5. On the basis of similarities in the phenotype of the mutant LRP6 embryos and embryos with mutant Wnt genes, Pinson et al. speculate that "our results support a role for **LRP6** in the transduction of several Wnt signals in mammals. (Pinson et al., col. 2, page 525, emphasis added.) The only comment Pinson et al. makes about LRP5 is that "LRP5 is widely expressed in embryos, and may limit the range and severity of Wnt phenotypes observed in LRP6-/-mice" , i.e., in mice that died at birth. (See 1st col., page 537 of Pinson et al.)

As one of ordinary skill in the cell biology art would understand and appreciate, 71% homology between two proteins is insufficient to reasonably predict that the two proteins would have the same binding partners. Moreover, and perhaps more importantly, a 71% sequence homology between two proteins is insufficient for one of ordinary skill in the art to reasonably predict whether binding of a particular ligand to both proteins would have the same effect, i.e., that such a ligand would activate both proteins. Thus, one of ordinary skill in the art, upon reading Pinson et al. would understand and appreciate that the statements made in Pinson et al. about the relationship between Wnt and LRP6 cannot be used to reasonably predict that Wnt and LRP5 would have the same relationship.

In addition, Pinson is directed to the effect of LRP6 in embryonic development and organogenesis. Pinson et al does not provide any guidance about the role, if any, that LRP6, plays postnatally in differentiated osteoblasts of live animals. Pinson et al. does not teach or suggest that LRP6, much less LRP5, is a signal transducer for Wnt in osteoblasts or bone forming cells in any cell, much less bone forming cells, of an animal after birth. In other words, there is nothing in Pinson et al. to suggest that LRP6, much less LRP5, would act as a signal transducer for Wnt in bone forming cells of patients with osteoporosis.

As stated in the Manual of Patent Examining Procedure (M.P.E.P. § 2142), to establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some

suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on Applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

In the instant case, one of ordinary skill in the art who is aware of the teachings in both Carulli et al. and Pinson et al. would not be motivated to combine the two references. Carulli et al. and Pinson et al. are directed to studies done on two different proteins. Moreover, one of ordinary skill in the art, upon reading Carulli et al. and Pinson et al. would not be motivated modify the general teachings in Carulli et al. about potential inhibitors and binding partners and to administer to patients with osteoporosis amounts of the effectors recited in claim 30, as amended, sufficient to increase alkaline phosphatase activity in bone forming cells. Carulli et al. does not identify any molecules that bind to BSMR in bone forming cells or provide any guidance as to which of these molecules would increase, as opposed to decrease, bone development in patients with osteoporosis. Similarly, Pinson et al. does not identify any molecules that act as effectors of BSMR and that increase alkaline phosphatase activity in osteoblasts. Thus, even if one combined Caulli et al. and Pinson et al., one would not arrive at all the steps in claim 30 or 32. Moreover, one of ordinary skill in the art who is aware of the teachings in both Carulli et al. and Pinson would not reasonably expect that administration of a WNT protein to a patient with osteoporosis would have a beneficial effect on bone development and mineralization in such individuals. Accordingly, Caurlli et al. and Pinson et al. do not render the methods recited in claim 30 and 32 as amended obvious.

Applicants submit that claims 8, 9, 30, 32-36 and new claims 37-38 are now in condition for allowance. Prompt notice of such allowance is respectfully requested. If the Examiner has any questions regarding the amendments, he is encouraged to call the undersigned at the number listed below.

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